Suppression of leukemia development caused by PTEN loss.

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Public Summary:
Multiple genetic or molecular alterations are known to be associated with cancer stem cell formation and cancer development. Targeting such alterations, therefore, may lead to cancer prevention. By crossing our previously established phosphatase and tensin homolog (Pten)-null acute T-lymphoblastic leukemia (T-ALL) model onto the recombination-activating gene 1(-/-) background, we show that the lack of variable, diversity and joining [V(D)J] recombination completely abolishes the Tcralpha/delta-c-myc translocation and T-ALL development, regardless of beta-catenin activation. We identify mammalian target of rapamycin (mTOR) as a regulator of beta-selection. Rapamycin, an mTOR-specific inhibitor, alters nutrient sensing and blocks T-cell differentiation from CD4(-)CD8(-) to CD4(+)CD8(+), the stage where the Tcralpha/delta-c-myc translocation occurs. Long-term rapamycin treatment of preleukemic Pten-null mice prevents Tcralpha/delta-c-myc translocation and leukemia stem cell (LSC) formation, and it halts T-ALL development. However, rapamycin alone fails to inhibit mTOR signaling in the c-Kit(mid)CD3(+)Lin(-) population enriched for LSCs and eliminate these cells. Our results support the idea that preventing LSC formation and selectively targeting LSCs are promising approaches for antileukemia therapies.

Scientific Abstract:
Multiple genetic or molecular alterations are known to be associated with cancer stem cell formation and cancer development. Targeting such alterations, therefore, may lead to cancer prevention. By crossing our previously established phosphatase and tensin homolog (Pten)-null acute T-lymphoblastic leukemia (T-ALL) model onto the recombination-activating gene 1(-/-) background, we show that the lack of variable, diversity and joining [V(D)J] recombination completely abolishes the Tcralpha/delta-c-myc translocation and T-ALL development, regardless of beta-catenin activation. We identify mammalian target of rapamycin (mTOR) as a regulator of beta-selection. Rapamycin, an mTOR-specific inhibitor, alters nutrient sensing and blocks T-cell differentiation from CD4(-)CD8(-) to CD4(+)CD8(+), the stage where the Tcralpha/delta-c-myc translocation occurs. Long-term rapamycin treatment of preleukemic Pten-null mice prevents Tcralpha/delta-c-myc translocation and leukemia stem cell (LSC) formation, and it halts T-ALL development. However, rapamycin alone fails to inhibit mTOR signaling in the c-Kit(mid)CD3(+)Lin(-) population enriched for LSCs and eliminate these cells. Our results support the idea that preventing LSC formation and selectively targeting LSCs are promising approaches for antileukemia therapies.

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